



AMERICAN
SOCIETY FOR
MICROBIOLOGY

Public and Scientific Affairs Board

July 30, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Critical Path Initiative [Docket No. 2004-N-0181]

The American Society for Microbiology (ASM) is pleased to respond to the Food and Drug Administration's (FDA) request for input on issues related to identifying and prioritizing the most pressing medical product development problems, medical product opportunities and the FDA Critical Path Initiative. The ASM is the largest single life science society, representing over 42,000 members who are involved in research and development in academic, clinical, industrial and government institutions.

The *Critical Path Initiative* offers many opportunities to enhance discovery and development of drugs, vaccines, and diagnostics for infectious agents. If implemented, specific aspects of the initiative not only will improve safety and efficacy but should contribute to reduction in the time and costs associated with the high risks and complexity of product development. For the ASM this is particularly important. The recent report *Microbial Threats to Health* released by the Institute of Medicine in March 2003 declared antimicrobial and vaccine development to be in a state of crisis based upon the status of the current pipeline for both naturally occurring infectious agents as well as for those that might be intentionally released in a bioterror attack. Thus for infectious diseases the FDA's *Critical Path Initiative* is very timely.

General Comments

The overall goals outlined in the initiative are laudable and should be pursued. The challenge will be to identify those gaps that are most relevant to speeding translation and not duplicative of those already ongoing at NIH. Thus, close coordination and planning with NIH will be necessary to leverage the best of both. In the area of infectious diseases this is particularly important post 9/11 with the National Institute of Allergy and Infectious Diseases having received an increase of \$1.7 billion specifically for

development of urgently needed countermeasures for bioterrorism, including drugs (antivirals and antibacterials), vaccines and diagnostics. At the same time it represents a unique opportunity to change the *status quo* given the speed with which these countermeasures must be developed and the necessity of application of the Animal Rule for regulatory approval. The current environment is also unique because of the degree that academic based scientists funded by NIAID are focusing on broad aspects of product development not only basic research. Thus as priorities are being established and a blue print for action being developed, it will be extremely important that FDA be engaged not only with industry but also academia and government scientists. In fact we would recommend that FDA should play a lead role in enhancing the interactions of the three sectors in order to speed product development and enhance the chances for success. In view of this ASM would like to co-host a forum with FDA to refine the priorities specific for product development related to infectious agents. In the interim we offer the following specific comments.

Specific Comments:

1. Clinical trials. One of the biggest hurdles for development of antimicrobials, particularly antibiotics, is the complexity and size of clinical trials required for regulatory approval in the U.S. and at the same time marked differences from criteria of regulatory agencies outside the U.S. Emphasis should be given to harmonization of international guidelines and flexibility concerning the evidence necessary to demonstrate safety and efficacy particularly as it relates to data required for different indications for the same infectious agent.

Regarding the development of vaccines, the recent rotavirus vaccine experience argues that much more thought needs to be given to the risk benefit ratio of products and the acceptable level of risk and actual numbers of patients practical to demonstrate an acceptable level of risk. Withdrawal of the rotavirus vaccine following a very small percentage of adverse events in the U.S., thousands of infants died outside the U.S. from rotavirus infection.

A recent assessment of barriers to clinical research revealed one of the biggest barriers to be lack of electronic medical records and easy access to data. This is essential in order to further demonstrate the need for new antibiotics and to facilitate tracking of antimicrobial resistance to clinical outcome.

2. Pharmacogenomics. Another hurdle to development of antimicrobials is related to toxicity, particularly antivirals. As a result of “data mining” and establishment of relational databases, it should be possible to establish more reliable predictors of toxicity. FDA is uniquely positioned to do this.

3. Manufacturing. Innovation in manufacturing has not kept pace with that in the discovery and clinical development phases. This is in part due to the lack of investment of public funds in this area of research. Opportunities for research gaps should be identified and funding sought in the public and private sectors. The same might be said for innovation in formulation. Concurrently, new and improved technologies that already exist should be adapted, specific examples include methods used to screen for adventitious microbial agents and endotoxin.

4. Diagnostics. When relevant, approval of diagnostics should be integrated with drug approval. The combination could reduce the inappropriate use of antibiotics and antivirals and thus slow development of resistance. Clear guidelines should be established for development of diagnostics for infectious agents including collection and processing of specimens. Given the financial resources, FDA could provide standards and well characterized control (negative and positive) specimens.

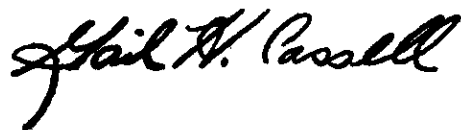
5. Development of Biothreat Countermeasures. In development of countermeasures for biothreat agents we are moving into uncharted waters. As the FDA begins to implement the animal rule; review of increased numbers of biologic products and vaccines; and immunomodulators in relation to review of biothreat countermeasures, it will be important to mine aggregate data for lessons learned and to be able to share the information so as to reduce unnecessary duplication of work and to speed product development. In addition, best practices and lessons learned in this area should be shared to enhance drug discovery and development for naturally occurring infectious agents.

The ASM looks forward to continued interactions with FDA on the *Critical Path Initiative* to develop a more detailed strategy and appreciate the opportunity to be involved in such an important undertaking.

Sincerely,



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Chair, Public and Scientific Affairs Board



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